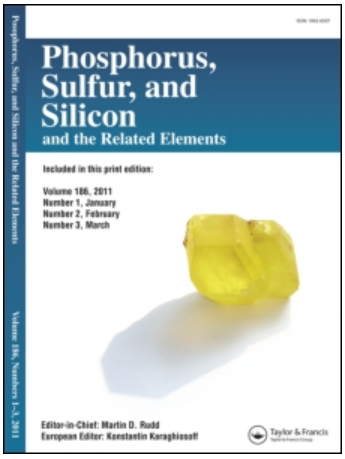

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NEW PRODUCTS OF REACTION OF LAWESSON'S REAGENT WITH DIOLS

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NEW PRODUCTS OF REACTION OF LAWESSON'S REAGENT WITH DIOLS

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*Reaction of the Lawesson's reagent (LR) with aliphatic 1,2- and 1,3-diols as well as with aromatic 2,2′-dihydroxybiphenyl led to new products. Stable di-*tert*-butylammonium salts of* bis-*anisyldithiophosphonic acids* ***6*** *were isolated and were then converted into unique 9-, 9-, and 10-membered cyclic disulfides* ***7*** *and into* S,S-*dimethyl esters* ***8****. The salts of* bis-*anisyldithiophosphonic acids* ***6*** *were shown to be capable of splitting the disulfide bond of Ellman's reagent.*

Keywords: *Bis*-anisyldithiophosphonic acids derivatives; diols; Lawesson's reagent

INTRODUCTION

The reaction between 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetan-2,4-disulfide (Lawesson's reagent, LR) and aliphatic[1] and aromatic[2] diols **1** were investigated earlier by Shabana. Contrary to his expectations, Shabana did not isolate *bis*-anisyldithiophosphonic acids **2** from the reaction mixture, but only the products of elimination of hydrogen sulfide, i.e., the corresponding heterocyclic compounds, namely 2,4-dianisyl-1,5,3,2,4-dioxathiadiphosphepane 2,4-disulfide **3**, 2-anisyl-1,3,2-dioxaphospholane 2 sulfide **4**, and 6-anisyldibenzo[d,f][1,3,2]dioxaphosphepine 6-sulfide **5** (Scheme 1). The reaction with aromatic diols run in boiling toluene led exclusively to cyclic anisylphosphonothioates. Undoubtedly, such reaction direction was forced by deliberate or unintentional application of elevated temperature and acetonitrile as solvent. Acetonitrile proved to be a good H_2S acceptor, and additionally, the widely known readiness of diol

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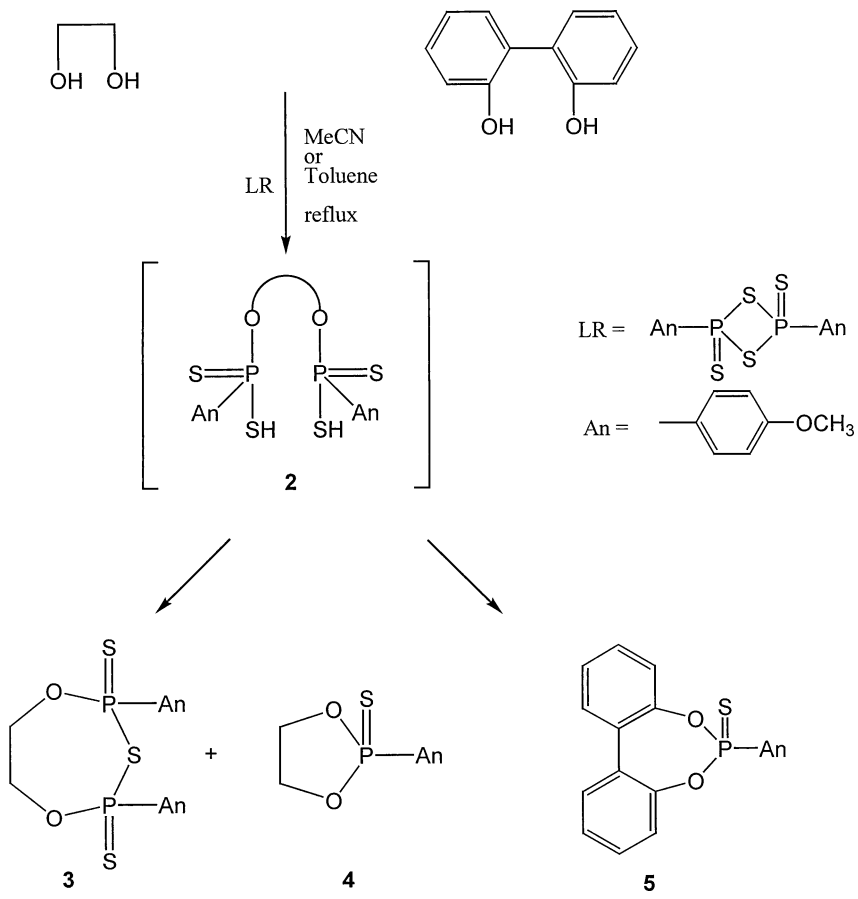


SCHEME 1

derivatives to undergo intramolecular cyclization[3] led to the synthesis of the 5- and 7-membered rings described above.

One should note that *bis*-dithiophosphonic acids were successfully obtained by Kutyrev et al.[4] and Navech et al.[5] by reacting diols with 2,4-bis(methyl)-1,3,2,4-dithiadiphosphetan-2,4-disulfide (*P*-methyl analogue of Lawesson's reagent) and with stable 2,4,6-tri-*tert*-butylphenyldithiophosphate, respectively.

Metal complexes with sulfur ligands are of special importance as models for investigating biological metal–sulfur interactions.[6] Due to synthetic difficulties, literature on dithiophosphonate chemistry is not as comprehensive as is the case with their analogues, i.e., dithiophosphates and dithiophosphinates, although diverse applications of

dithiophosphonates in industry and agriculture are highly valued.[7] Recently, more attention has been paid to physicochemical properties of complexes of anisyldithiophosphonic acids synthesized in reactions of LR with alcohols.[8] *Bis*-dithiophosphonic acids are particularly interesting in this respect, since as bidentate chelating ligands they are able to produce much more stable complexes with metal ions.

Moreover, if *bis*-dithiophosphonic acids proved to be able to form cyclic disulfides, they could potentially be used in thiol-disulfide interchange reaction—a process of great biochemical significance.[9] As reported in the literature, the dithiols capable of oxidation to cyclic disulfides are the fastest to split disulfide bonds.[10] Furthermore, a conceivable advantage of *bis*-dithiophosphonic acids results from their acidic character, which allows them to operate at lower pH than is the case for the widely used dithiols.

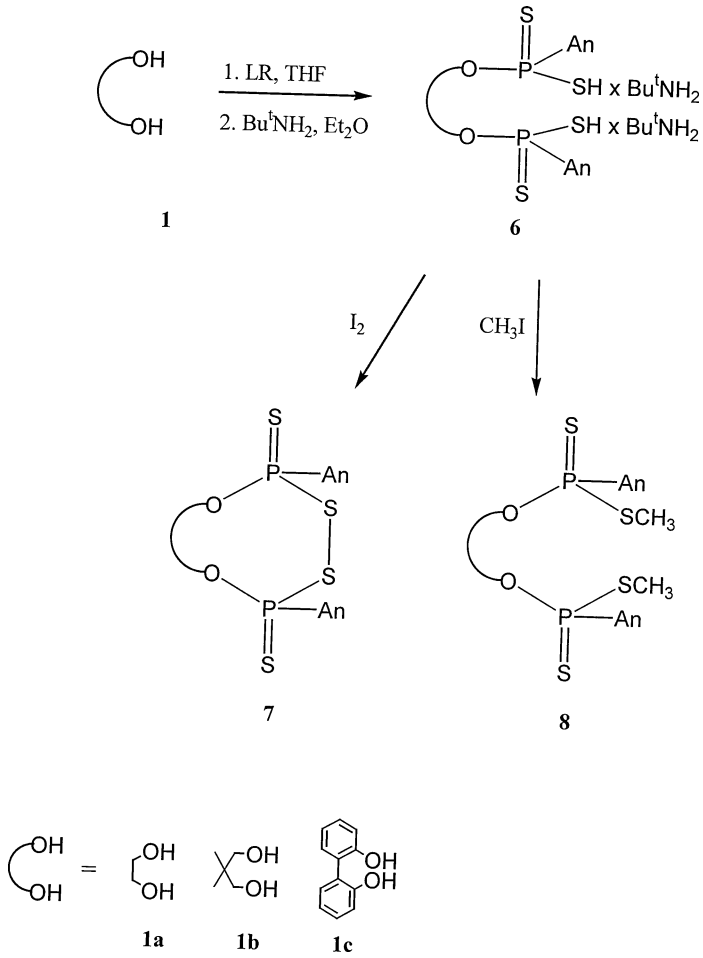
In order to test the potential avenues for application of *bis*-dithiophosphonic acids, I attempted to synthesize them. To that end, I decided to reinvestigate the reaction of LR with diols.

RESULTS AND DISCUSSION

Fortunately, when the reaction of diols with LR is run at room temperature, corresponding adducts, i.e., *bis*-anisyldithiophosphonic acids **2** are formed, which I have isolated as di-*tert*-butylammonium salts **6** with high yields (Scheme 2). The range of their ^{31}P chemical shifts corresponds to the structure of anisyldithiophosphonic acid ester salts.[11] In addition, salts **6** have been found to be crystalline, odorless, nonhygroscopic, and stable to air (they do not exhibit detectable changes after 7 months).

I suspected that oxidation of salts **6** could lead to formation of cyclic disulfides, an interesting and, to our knowledge, previously unknown class of compounds; however I could not exclude the possibility of polymeric disulfides forming in this reaction.

Upon treatment with iodine in tetrahydrofuran (THF), the salts **6** turned out, however, to form disulfides **7** with good yields (61–67%). A fact of particular importance is that the reaction of forming these medium-sized disulfide rings does not need to be run in high dilution and leads to formation of insignificant amounts of dimers and oligomers. Unfortunately, attempts to obtain monocrystals of disulfides **7** suitable for X-ray structural analysis were not successful. Nuclear magnetic resonance (NMR) (Figure 1) and mass spectrometry (MS) were employed for elucidating the structure of this new class of compounds. Detailed NMR analysis showed that the cyclic



SCHEME 2

8-membered disulfide **7a** forms a rigid ring. At room temperature, it shows no conformational freedom in solution. Aliphatic ring protons in **7a** form a complex spin–spin system and additionally couple with nonequivalent phosphorus atoms. The relatively small coupling constant between phosphorus atoms ($^3J_{PP}$ = 4 Hz) additionally confirms the presence of the P-S-S-P system[12] in these compounds.

Salts **6** were then successfully converted with good yields to *S*,*S*-dimethyl diesters **8a**,**b** upon treatment with methyl iodide. Obtaining derivatives **8** constitutes an additional proof of the structure of salts **6** obtained in reaction of diols with LR. The observed range of ^{31}P chemical

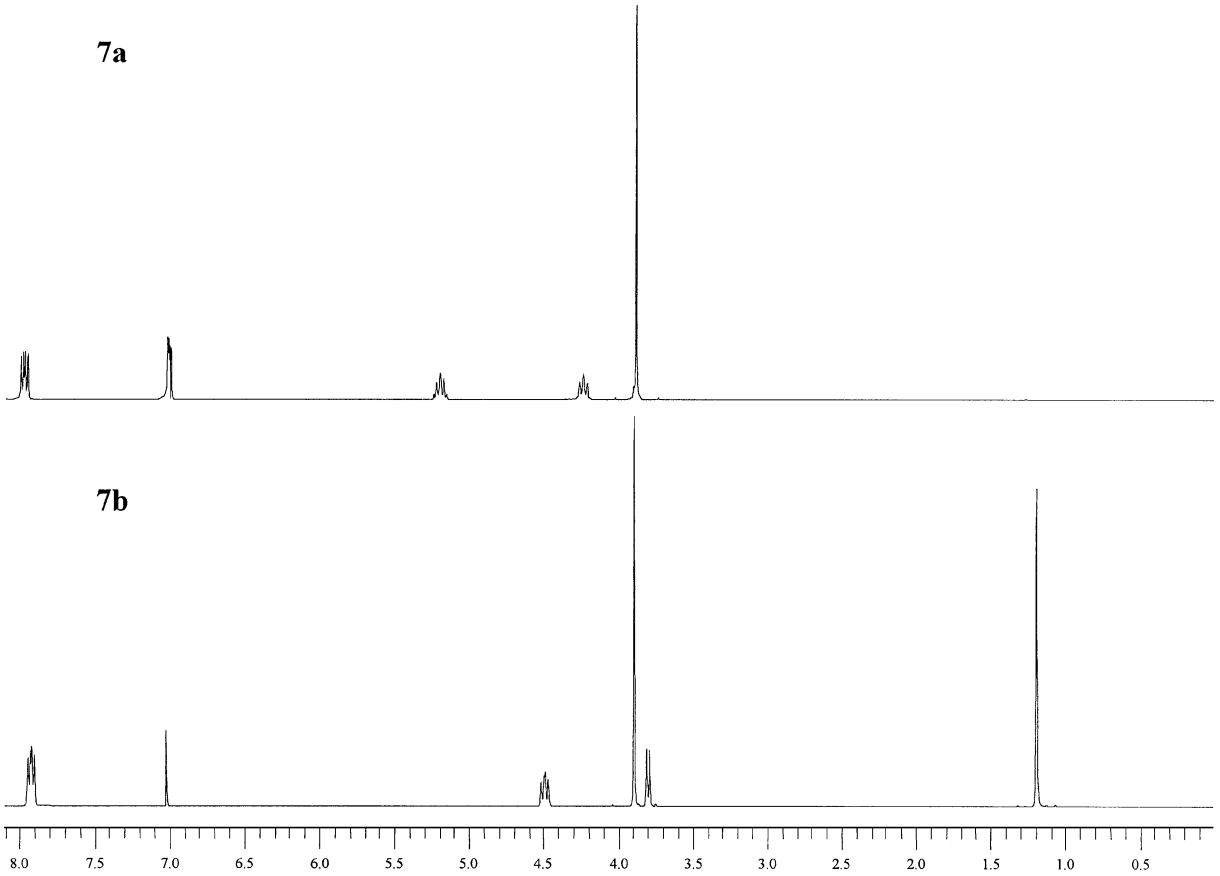


FIGURE 1 ^{1}H NMR spectra of disulfides **7a** and **7b**.

shifts (95.5–99.8 ppm) corresponds to the structure of *S*-methyl esters of *O*-alkylanisyldithiophosphonic acid (for comparison, the chemical shift for AnP(S)SMeOMe: $\delta_{31P} = 99.9$ ppm). As expected, the obtained diesters **8** are mixtures of diastereomers (Figure 2).

Analysis of ^{1}H, ^{13}C, and ^{31}P NMR spectra confirms that **8a** and **8b** were obtained as diastereoisomer pairs in approximately equal amounts, while **8c** is a mixture of several diastereomers (three centers of chirality are present) of random populations.

Since the rotation barrier in the biphenyl system disappears, the ^{1}H NMR spectrum of **8c** at 80°C simplifies, and only signals of four diastereomers are observed (Figure 3).

The following observed interesting fragmentations of derivatives **7** and **8** in MS spectra are especially noteworthy. The most intense peak in the MS spectra of disulfide derivatives of aliphatic diols **7a** and **7b** appears at m/z 262 and 304, respectively, which corresponds to the loss of anisyldithiophosphonate (m/z 202) from the molecular ions. In the case of disulfide **7c**, the main peak at m/z 184 corresponds to stable aromatic dioxobiphenyl ion, which is formed upon loss of both anisyldithiophosphonate residues.

A characteristic feature of the MS spectra of all obtained *S,S*-dimethyl esters **8** is the presence of the main peak at m/z 217 corresponding to *S*-methylanisyldithiophosphonate ion.

A question remains of whether the obtained derivatives of *bis*-anisyldithiophosphonic acids **6** and **7** will be able to participate in thiol-disulfide interchange reactions. Analytic tests showed that salts **6** efficiently split S–S bonds in Ellman's reagent[13] at pH 8, instantly producing intensive yellow color due to the formation of 5-mercapto-2-nitrobenzoic acid thiolate. Therefore, the salts of *bis*-anisyldithiophosphonic acids **6** emerge as relatively cheap, stable, and odorless substitutes of widely used dithiols, including dithiotreitol (DTT).

The reaction of LR with other diols, including phenoloalcohols, is under investigation, and the results will be published subsequently.

EXPERIMENTAL

^{1}H and ^{31}P NMR spectra were recorded in $CDCl_3$ on a Varian 500 MHz spectrometer with tetramethylsilane (TMS) and H_3PO_4 as internal standard, respectively. MS spectra (EI, 70 eV) were measured with a AMD 604 mass spectrometer (AMD Intectra GmbH, Germany). Reactions were monitored and homogeneity of products was checked by thin layer chromatography (TLC) on silica gel 60 (Merck, Art.5724) with chloroform.

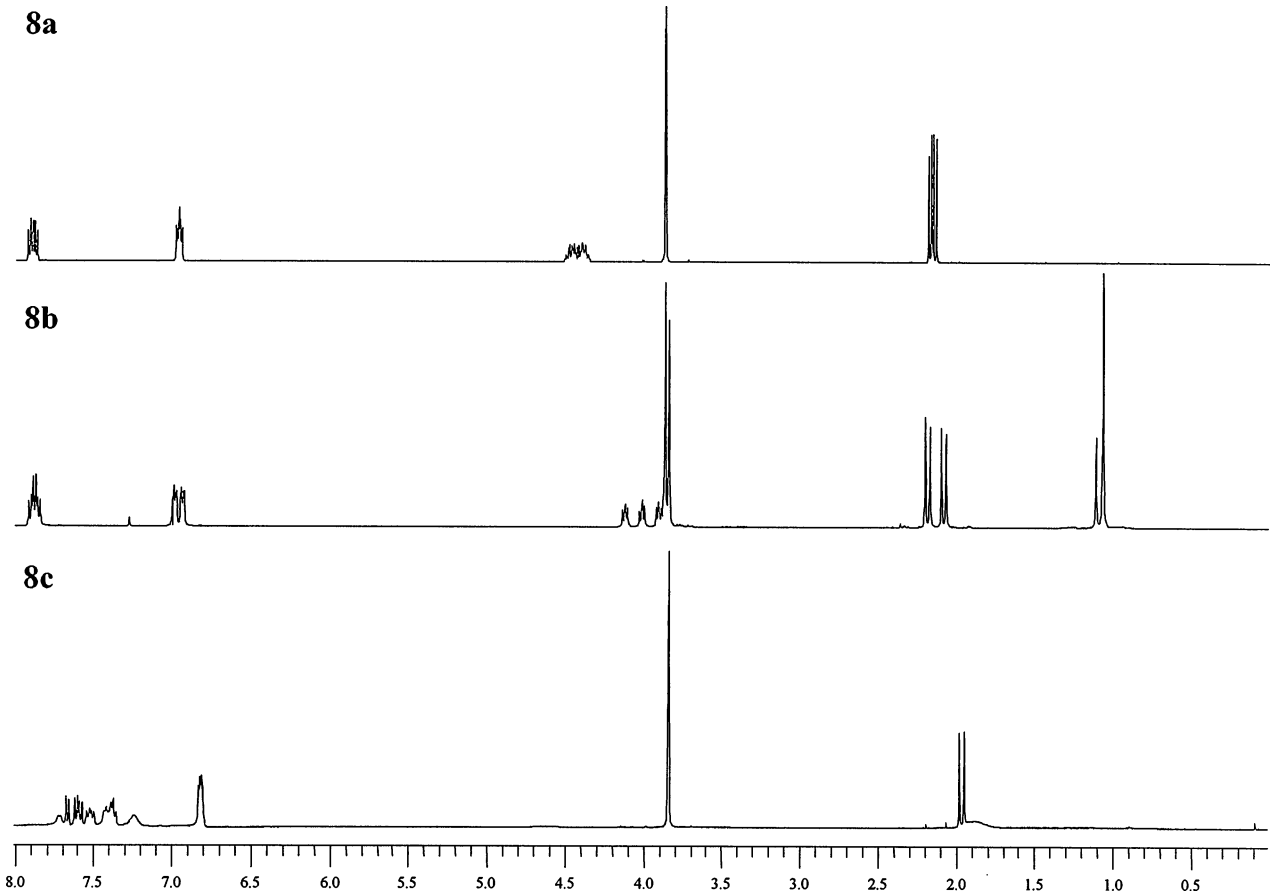


FIGURE 2 ^{1}H NMR spectra of *S,S*-dimethyl esters **8a–c**.

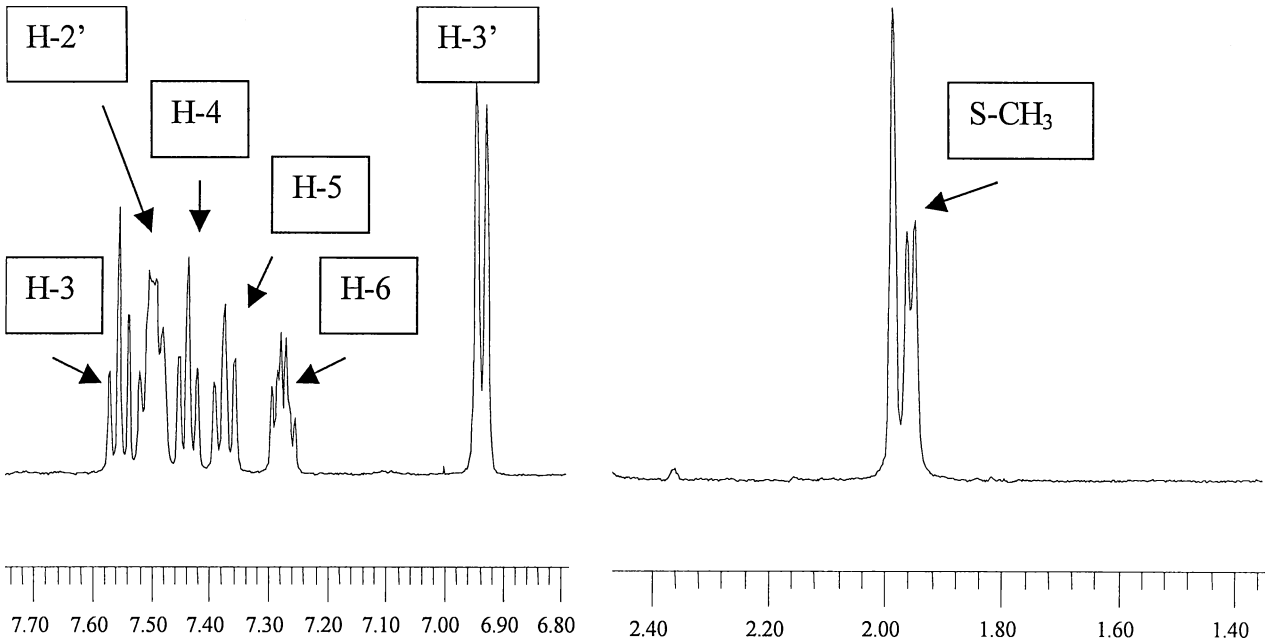


FIGURE 3 ^{31}P-decoupled ^{1}H NMR spectrum of **8c** recorded at 80°C.

THF was distilled from potassium-benzophenone ketyl, and LR (Lancaster) was recrystallized from chlorobenzene prior to use. Ethylene glycol, 2,2-dimethyl-1,3-propanediol and 2,2′-dihydroxybiphenyl were commercially available (Lancaster). All reactions were performed under an atmosphere of argon in flame-dried flasks equipped with a stir bar and a rubber septum.

Ditertbutylamonium Bisdithiophosphononates (6a–c)

General Procedure

To a stirred solution of the corresponding diol **1** (1 mmol) in THF (4 ml), LR (0.404 g, 1 mmol) was added in one portion at room temperature. After 15 min when the mixture became homogenous it was concentrated in vacuo. The residue was dissolved in diethyl ether (5 ml), and *tert*butyl amine (0.21 ml, 2 mmol) was added dropwise. The resulting white solid (excluding **6c**) was filtered and dried over P_4O_{10}. In the case of **6c** the solvent was decanted from a viscous syrup, and the product was crystallized from benzene-hexane.

Ditertbutylamonium 1,2-Dioxoethane-1,2-bis[(4-methoxyphenyl)dithiophosphonate (6a)

0.57 g (93%); m.p., 160–163°C; ^{1}H NMR ($CDCl_3$, ppm): 1.55 (s, 18H, CH_3), 3.82 (s, 6H, OCH_3), 3.85 (m, 4H, OCH_2), 6.87 (dd, 4H, $^4J_{PH}$ = 2.44 Hz, $^3J_{HH}$ = 8.79 Hz), 8.02 (dd, 4H, $^3J_{PH}$ = 13.20 Hz, $^3J_{HH}$ = 8.79 Hz), 8.05 (m, 6H, NH_3^+); $^{31}P\{^1H\}$ δ 109.0 ppm.

Ditertbutylamonium 2,2-Dimethyl-1,3-dioxopropane-1,3-bis[(4-methoxyphenyl)dithiophosphononate (6b)

0.63 g (98%); m.p., 181–184°C; ^{1}H NMR ($CDCl_3$, ppm): 0.74 (s, 6H, CH_3), 1.57 (s, 18H, CH_3), 3.44 (d, 4H, $^2J_{HH}$ = 5.86 Hz), 3.83 (s, 6H, OCH_3), 6.90 (dd, 4H, $^4J_{PH}$ = 2.4 Hz, $^3J_{HH}$ = 8.8 Hz), 8.02 (dd, 4H, $^3J_{PH}$ = 13.7 Hz, $^3J_{HH}$ = 8.8 Hz), 8.14 (br s, 6H, NH_3^+); $^{31}P\{^1H\}$ δ 105.1 ppm.

Ditertbutylamonium 2,2′-Dihydroxybiphenyl-O,O′-bis[(4-methoxyphenyl)dithiophosphonate (6c)

0.23 g (31%); m.p., 155–166°C; ^{1}H NMR ($CDCl_3$, ppm): 1.33 (s, 18H, CH_3), 3.83 (s, 6H, OCH_3), 6.86 (dd, 4H, $^4J_{PH}$ = 2.4 Hz, $^3J_{HH}$ = 8.8 Hz), 7.15 (2xt, 4H, J = 7.8, H-4/4′ and H-5/5′), 7.26 (d, 2H, J = 7.8, H-3/3′), 7.50 (d, 2H, J = 7.8, H6/6′), 7.97 (dd, 4H, $^3J_{PH}$ = 14.2 Hz, $^3J_{HH}$ = 8.8 Hz); $^{31}P\{^1H\}$ δ 109.1 ppm.

Disulfides (7a–c)

General Procedure

To a stirred solution of disalt **6** (0.1 mmol) in ethyl acetate (3 ml) and THF (2 ml), iodine (0.06M solution in THF, 1.69 ml) was added dropwise with ice-cooling. Evaporation of the solvents in vacuo at 20°C, followed by chromatography on a silica gel column (12 × 1 cm, chloroform) yielded **7a** and **7b** as white solids. Insoluble biphenyl derivative **7c** was directly filtered off from the reaction mixture and was washed thoroughly with THF.

2,5-Di(4-methoxyphenyl)-[1,6,3,4,2,5]-dioxadithiadiphosphocane 2,5-Disulfide (7a)

R_f 0.54; 0.029 g (62%); m.p., 168–170°C; ^{1}H NMR ($CDCl_3$, ppm): 3.88 (s, 6H, OCH_3), 4.24 (m, 2H, $^2J = 13.3$, $^3J_{ee} = 1.62$, $^3J_{ea} = 1.58$, $^3J_{P1e} = 14.9$, $^4J_{P2e} = 0.92$, H-equatorial), 5.20 (m, 2H, $^2J = 13.3$, $^3J_{aa} = 10.38$, $^3J_{ea} = 1.58$, $^3J_{P1a} = 18.5$, $^3J_{P2a} = 3.09$, $^4J_{P2e} = 0.92$, H-axial), 7.00 (dd, 4H, $^4J_{PH} = 3.42$ Hz, $^3J_{HH} = 8.79$ Hz), 7.98 (dd, 4H, $^3J_{PH} = 14.17$ Hz, $^3J_{HH} = 8.79$ Hz); ^{13}C: 55.8 (C-7′), 65.2 (C-1), 114.3 (d, $J = 17.6$ Hz, C-3′/5′), 125.7 (d, $J = 135$ Hz, C-1′), 133.1 (d, $J = 13.7$ Hz, C-2′/6′), 163.6 (C-4′); ^{31}P{^{1}H} δ 88.04 ppm; MS, m/e (I_{rel}, %): 464 $[M]^{+\cdot}$(10), 400 $[M\text{-}S_2]^{+\cdot}$(3), 262 $[M\text{-}AnPS_2]^{+\cdot}$(88), 246 $[M\text{-}AnPS_2O]^{+\cdot}$(100), 202 $[AnPS_2]^{+\cdot}$(36), 187 $[AnPSO + 1]^+$ (74), 139 $[AnP + 1]^+$ (71%); HRMS (EI): Calc. for $C_{16}H_{18}O_4S_4P_2$ 463.95632. Found 463.95813.

2,5-Di(4-methoxyphenyl)-8,8-dimethyl-[1,6,3,4,2,5]-dioxadithiadiphosphonane 2,5-Disulfide (7b)

R_f 0.67; 0.034 g (67%); m.p., 179–180°C; ^{1}H NMR ($CDCl_3$, ppm): 1.19 (s, 6H, CH_3), 3.80 (dd, $2H_e$, $^2J = 10.0$ Hz, $^3J_{PH} = 1$ Hz, H-equatorial), 3.89 (s, 6H, OCH_3), 4.49 (dd, $2H_a$, $^2J = 10.0$ Hz, $^3J_{PH} = 13.7$ Hz, H-axial), 7.03 (dd, 4H, $^4J_{PH} = 3.42$ Hz, $^3J_{HH} = 8.79$ Hz), 7.93 (dd, 4H, $^3J_{PH} = 13.67$ Hz, $^3J_{HH} = 8.79$ Hz); ^{13}C: 21.8 (C-3), 36.5 (C-2), 55.8 (C-7′), 69.6 (C-1), 114.4 (d, $J = 17.5$ Hz, C-3′/5′), 124.6 (d, $J = 134$ Hz, C-1′), 133.4 (d, $J = 13.7$ Hz, C-2′/6′), 163.7 (C-4′); ^{31}P{^{1}H} δ 88.72 ppm; MS, m/e (I_{rel}, %): 506 $[M]^{+\cdot}$(11), 442 $[M\text{-}S_2]^{+\cdot}$(16), 304 $[M\text{-}AnPS_2]^{+\cdot}$(100), 288 $[M\text{-}AnPS_2O]^{+\cdot}$(41), 202 $[AnPS_2]^{+\cdot}$(38), 187 $[AnPSO + 1]^+$ (57), 139 $[AnP + 1]^+$ (65%); HRMS (EI): Calc. for $C_{19}H_{24}O_4S_4P_2$ 506.00327. Found 506.00407.

2,2′-Dihydroxybiphenyl-O,O′-bis[(4-methoxyphenyl)thiophosphonodisulfide (7c)

R_f 0.80; crude, 0.036 g (61%); m.p., 215–222°C; ^{31}P{^{1}H} δ 87.14 ppm; MS, m/e (I_{rel}, %): 588 $[M]^{+\cdot}$(1), 524 $[M\text{-}S_2]^{+\cdot}$(1), 386 $[M\text{-}AnPS_2]^{+\cdot}$(11), 202

$[AnPS_2]^{+\cdot}$(27), 184 $[M\text{-}2AnPS_2]^{+\cdot}$(100), 139 $[AnP + 1]^+$ (34%); HRMS (EI): Calc. for $C_{26}H_{22}O_4S_4P_2$ 587.98762. Found 587.98804.

General Procedure for Synthesis of Diesters (8a–c)

To a stirred solution of disalt **6** (0.1 mmol) in THF (1.5 ml) methyl iodide (0.012 ml, 0.2 mmol) was added with ice-cooling. After 1 h at room temperature the mixture was concentrated in vacuo. A residue was dissolved in ethyl acetate and washed with 2% $Na_2S_2O_3$ aqueous solution, twice with water, brine, and dried over $MgSO_4$. Concentration left the crude diester **8**, which was purified on a silica gel column with chloroform as an eluent to give the pure product **8** as a colorless oil.

1,2-Dioxoethane-1,2-bis[(4-methoxyphenyl)-dithiophosphonic Acid S,S-dimethyl Ester] (8a)

R_f 0.77; 0.042 g (85%); ^{1}H NMR ($CDCl_3$, ppm): 2.15 (d, 3H, $^3J_{PH}$ = 15.63 Hz, SCH_3), 2.17 (d, 3H, $^3J_{PH}$ = 15.17 Hz, SCH_3), 3.86 and 3.87 (2xs, 2x3H, OCH_3), 4.34–4.52 (m, 4H, OCH_2), 6.96 and 6.97 (2xdd, 4H, $^4J_{PH}$ = 3.42 Hz, $^3J_{HH}$ = 8.79 Hz), 7.89 and 7.91 (2xdd, 4H, $^3J_{PH}$ = 13.67 Hz, $^3J_{HH}$ = 8.79 Hz); ^{13}C: 15.4 (d, J = 14.5 Hz, SCH_3), 55.7 (C-7′), 64.18 and 64.23 (2xd, J = 6.9, C-1), 55.7 (C-7′), 114.2 and 114.3 (2xd, J = 16 Hz, C-3′/5′), 126.0 (d, J = 127 Hz, C-1′), 133.10 and 133.13 (2xd, J = 13.7 Hz, C-2′/6′), 163.1 (C-4′); ^{31}P{^{1}H} δ 99.0 and 99.8 ppm; MS, m/e (I_{rel}, %): 494 $[M]^{+\cdot}$(2), 447 $[M\text{-}SCH_3]^+$ (13), 261 $[M\text{-}AnPOSCH_3]^+$ (18), 217 $[AnPSSCH_3]^+$ (100), 201 $[AnPS_2]^+$ (26), 139 $[AnP + 1]^+$ (23); HRMS (EI): Calc. for $C_{18}H_{24}O_4S_4P_2$ 494.00327. Found 494.00552.

2,2-Dimethyl-1,3-dioxopropane-1,3-bis-[(4-methoxyphenyl)dithiophosphonic Acid S,S-dimethyl Ester] (8b)

R_f 0.63; 0.050 g (94%); ^{1}H NMR ($CDCl_3$, ppm): 1.07 (s, 3H), 1.07 and 1.11 (2xs, 3H), 2.08 (d, 3H, $^3J_{PH}$ = 14.65 Hz, SCH_3), 2.19 (d, 3H, $^3J_{PH}$ = 15.14 Hz, SCH_3), 3.84 and 3.86 (2xs, 2x3H, OCH_3), 3.87, 3.90, 4.01, and 4.12 (4xdd, 4H, J_1 = 9.5 Hz, J_2 = 6.5 Hz), 6.93 and 6.98 (2xdd, 4H, $^4J_{PH}$ = 3.42 Hz, $^3J_{HH}$ = 8.79 Hz), 7.86 and 7.89 (2xdd, 4H, $^3J_{PH}$ = 14.16 Hz, $^3J_{HH}$ = 8.78 Hz); ^{13}C: 15.47 and 15.50 (2xd, J = 14.5 Hz, SCH_3), 21.49, 21.58, 22.00, 22.14 (C-3), 36.30 and 36.45 (2xd, J = 8.4 Hz, C-2), 55.47 and 55.72 (C-7′), 69.4 and 69.9 (2xd, J = 6.9, C-1), 114.2 and 114.3 (2xd, J = 16 Hz, C-3′/5′), 126.0 (d, J = 127 Hz, C-1′), 133.0 and 133.1 (2xd, J = 13 Hz, C-2′/6′), 163.0 (C-4′); ^{31}P{^{1}H} δ 96.9 and 98.0 ppm; MS, m/e (I_{rel}, %): 536 $[M]^{+\cdot}$(6), 489 $[M\text{-}SCH_3]^+$ (28), 303 $[M\text{-}AnPOSCH_3]^+$ (2),

217 [AnPSSCH$_3$]$^+$ (100), 201 [AnPS$_2$]$^+$ (7), 187 [AnPSO + 1] (27), 139 [AnP + 1]$^+$ (26); HRMS (EI): Calc. for $C_{21}H_{30}O_4S_4P_2$ 536.05022. Found 536.05011.

2,2′-Dihydroxybiphenyl-O,O′-bis[(4-methoxyphenyl)dithiophosphonic Acid S,S-dimethyl Ester] (8c)

R_f 0.70; 0.028 g (45%); ^{1}H NMR ($CDCl_3$, ppm): 1.80–2.00 and 1.96 (br m and d, 6H, $^3J_{PH} = 15.6$ Hz, SCH_3), 3.83 and 3.84 (2xs, 2x3H, OCH_3), 6.81 (dd, 4H, $^4J_{PH} = 3.4$ Hz, $^3J_{HH} = 8.8$ Hz), 7.24 (br m, 2H), 7.34–7.44 (m, 4H,), 7.68 (d, 1H, $J = 8.3$ Hz,), 7.72 (br d, 1H, $J = 8.3$ Hz,), 7.52 and 7.59 (2xdd, 4H, $^3J_{PH} = 14.2$ Hz, $^3J_{HH} = 8.8$ Hz); ^{1}H{^{31}P} NMR (DMSO-d_6, 80°C, ppm): 1.94, 1.96 (2xs), 1.99 (2xs), 6.94 (2xd, H-3′), 7.27 (4xd, H-6), 7.37 (2xt, H-5), 7.43 (2xt, H-4), 7.49 (2xd, H-2′), 7.54, 7.56 (2xd, H-3); ^{13}C: 15.4 (SCH_3), 55.7 (C-7′), 114.0 and 114.1 (2xd, $J = 16$ Hz, C-3′/5′), 125.9 (d, $J = 127$ Hz, C-1′), 133.2 (d, $J = 13.8$ Hz, C-2′/6′), 148.9 (C-1), 163.0 (C-4′); ^{31}P{^{1}H} δ 95.5–97.5 ppm; MS, m/e (I_{rel}, %): 618 [M]$^{+\cdot}$(8), 571 [M-SCH$_3$]$^+$ (7), 385 [M-AnPOSCH$_3$]$^+$ (2), 217 [AnPSSCH$_3$]$^+$ (100), 184 [M-2AnPSSCH$_3$]$^{+\cdot}$(23), 139 [AnP + 1]$^+$ (12); HRMS (EI): Calc. for $C_{28}H_{28}O_4S_4P_2$ 618.03457. Found 618.03474.

Ellman's Reagent Reduction

To a solution of **6a** (47 mg, 0.1 mmol) in ethanol (1 ml) 5,5′-dithiobis(2-nitrobenzoic acid) (40 mg, 0.1 mmol) was added. Immediately, the solution becomes deep yellow, indicating that 5-thio-2-nitrobenzoic acid anion is formed. The same result was obtained in buffer solution pH 8.0.

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